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(A) SCIENTIFIC ABSTRACT

Psoriatic arthritis (PsA) is an inflammatory joint disease common in individuals with psoriasis, affecting approximately 30% of all patients (1). Early intervention in PsA is disease modifying and a delay in diagnosis by as little as six months is associated with substantially lower treatment response (2). Nevertheless, diagnosis is frequently delayed and the median time from onset of symptoms to diagnosis has been estimated at 2.5 years (3). One of the key reasons for lack of a predictive algorithm for PsA is the lack of prospective studies from psoriasis onset.

The Stockholm Psoriasis Cohort (SPC) is a prospective inception cohort study that enrolled patients with psoriasis within one year of first disease onset in the Stockholm area, Sweden (4). Patients were followed- up clinically at 5 and 10 years. The study started in 2000 and enrolled 753 patients and up to six age, sex, and post-code matched controls. Data on patient history, life-style factors, genotype, phenotype, systemics inflammation, and metabolomics were obtained. The study was also linked to Swedish administrative registers to complement data from the examinations. To the best of our knowledge, the SPC is the only study that has prospectively followed patients with psoriasis from disease onset Given the rich data and its prospective follow-up from disease onset, the SPC presents a unique opportunity to derive a predictive algorithm for the development of PsA. Reflecting the substantial number of candidate variables, traditional statistical methods requiring pre-specification are not ideally suited for this task, instead we intend to use statistical learning techniques to derive an algorithm.

(B) LAY ABSTRACT

Psoriatic arthritis (PsA) is an inflammatory joint disease affecting approximately 30% of all patients with psoriasis (1). Early detection and treatment of PsA improves the disease course and a delay in diagnosis by as little as six months results in lower treatment response (2). However, detection of PsA is often delayed and the average time from onset to diagnosis is 2.5 years. We intend to analyze data from the Stockholm Psoriasis Cohort (SPC), a study that followed patients over ten years from first onset of psoriasis (4). The study has very detailed data on genetics, biomarkers, skin and joint symptoms, life-style factors, and comorbidities for 753 patients. Applying novel statistical learning techniques to data from the SPC affords a unique opportunity to derive a predictive algorithm for the development of PsA at psoriasis onset. Such an algorithm would allow for earlier detection of PsA, improving long term outcomes for patients with this potentially debilitating disease.

(C) BACKGROUND

Psoriatic arthritis (PsA) is an inflammatory joint disease common in individuals with psoriasis, affecting approximately 30% of all patients with psoriasis (1). The disease is heterogeneous in its clinical presentation and disease course, but many patients develop a destructive form of arthritis with substantial morbidity and disability (1). There has been a rapid growth in the treatment armamentarium for psoriasis in recent years but these accomplishments are yet to be matched in PsA, for which new therapies have not demonstrated superiority over established treatments (5).

Early intervention in PsA is disease modifying and a delay in diagnosis by as little as six months is associated with substantially lower treatment response, whereas early intervention with immune-modulating or anti-inflammatory drugs considerably improves outcomes (3). Most patients (80-90%) are diagnosed after the onset of skin lesions in psoriasis and there is a window of opportunity for modifying the disease course with effective treatment (1). However, PsA is frequently underdiagnosed, especially in dermatology settings and substantial diagnostic delay is also common (4) (5). One of the key reasons for these short-comings is the lack of prospective studies from onset of psoriasis: The knowledge on risk factors for PsA are limited. Therefore, in this grant application we seek funding to expand on previous analysis from The Stockholm Psoriasis Cohort (SPC) – to the best of our knowledge the only existing inception cohort study in psoriasis. We have previously demonstrated that a combination of basic clinical characteristic has good discriminatory power for identifying patients who will develop PsA (Figure 1) at onset of psoriasis and we now want to incorporate blood-based biomarkers and further patient reported data to improve the algorithm.

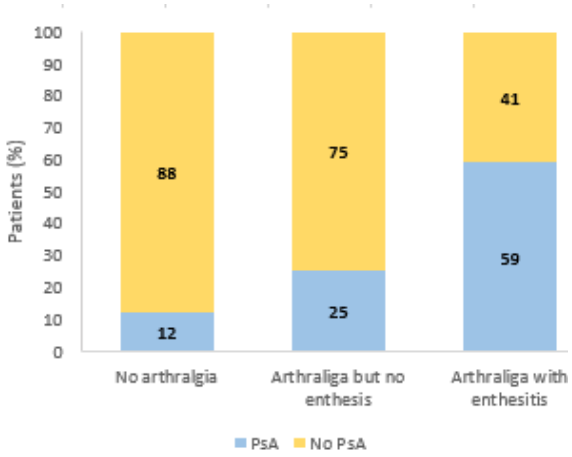

Figure 1 Psoriatic arthritis at ten years by arthralgia and enthesitis at onset of skin disease, preliminary results from the SPC

(D) METHODS

The SPC was a prospective observational study on patients with recent onset psoriasis and population matched controls. Patients above 15 years of age with first onset of psoriasis lesions on non-hairy skin within the last 12 months were eligible for study inclusion. The data collected in the SPC were complemented with data from medical records.

Study data

Patients and study data

Participants in the SPC were mainly recruited from the Stockholm area, Sweden, between 2000 and 2005. Patients were referred from dermatology clinics, general practitioners, school nurses, sexual health centers, and youth clinics. All patients had a detailed skin examination performed by a dermatologist. During follow-up, patients were examined clinically at five and ten years. In addition to the skin examination, patients with subjective joint problems were seen by a rheumatologist for comprehensive joint examination. All examinations were performed using standardized procedures and reporting.

In conjunction with the clinical examinations, patients competed an extensive questionnaire and blood were drawn. The questionnaire included items on inflammatory joint disease in parents, localization of pain (neck, shoulders, wrists/hands, upper back, lower back, hips or knees, and joints or ankles), sleep, general well-being, and life-style factors (smoking, alcohol consumption, exercise, and heavy lifting).

Genomic DNA was extracted by standard procedures. In collaboration with NIH, full genome sequencing on the participants has been performed. For this project, we will focus on the subset of variants located on the MHC in chromosome 6 previously associated with PsA (6). The reason is that no genome-wide significant loci discriminating between psoriasis with and without arthritis has been identified outside this region (6).

Blood was analyzed using standard lab tests, Nuclear Magnetic Resonance (NMR) spectroscopy, and a multi-assay cytokine panel. Furthermore, we are performing a robust ultra-performance liquid chromatography - tandem mass spectrometer (UPLC-MS/MS) method for simultaneous analysis of eight different tryptophan metabolites of the kynurenine pathway – a pathway that has been implicated in immune-mediated rheumatic disease (7).

For all study participant diagnoses and treatments for skin, joint and cardiovascular disease were obtained from the National Patient Register (8) and the Prescribed Drug Register. Causes of death were obtained from the Causes of death register and (9) migration data were obtained from the Total Population Register (10, 11). A summary of the of potentially relevant variables collected in the study are presented in Table 1 below.

Table 1 Selected candidate variables to be included in statistical learning models

Variable class	Type of variable
Genetics	Genetic variants on MCH chromosome 6 previously associated with PsA
Systemic inflammation	IL-17a, TNF-a, CRP, IL-6, SAA, GSCF, MCP-1, IFN-B, IL-1B, IL-23, IL-8, GlycA, ICAM-1, and VCAM-1
Tryptophan	Tryptophan, kynurenine-, kynurenic -, xanthurenic - and quinolinic acid, and nicotinamide
Onset triggers	Stress, Infection, other
Joint symptomology	Arthralgia (yes/no), peripheral enthesitis, location of arthralgia (nine regions), tenosynovitis
Anthropometrics	Weight, height
Life-style factors	Smoking, risk use of alcohol, exercise, and heavy lifting
Patient characteristics	Plaque, Guttate, Other, sex, age, family history of rheumatic disease
Comorbidities	Hospitalization for external injury, hospitalization for infection, PASI, scalp lesions, nail lesions

Exposure and Outcomes

Exposure, outcomes, and predictors

The main objective of this study is to derive an algorithm to identify PsA. Therefore, the exposures in the study will be variables that can be related to the development of PsA.

The main outcome in this study is PsA at ten years based on a specialist diagnosis, complemented with data from medical records and registers. We will sensitize the results by altering the definitions of PsA. Specifically, we will study PsA at 5 years, and by end of follow-up – with the latter outcome updating the ten-year outcome with register data.

Predictors will include factors that can reasonably be related to development of PsA.

Statistics

Basic descriptive statistics of the cohorts will be provided. Continuous variables will be reported using mean and standard deviation or median and interquartile ranges as appropriate. Categorical variables will be reported using frequencies and percentages. We will provide standardized differences to contextualize differences between groups.

To explore the association between PsA and key exposures, we will fit conventional univariable and multivariable logistic regression models with PsA as an outcome. Predictors for these analyses will include selected inflammatory markers (IL-17a, IL23, CRP, GlycA, and SAA), selected genetic variants, anthropometric measure (weight, height), localization of arthralgia, and rheumatic joint disease heritability, life-style factors, and onset triggers.

We will also explore use supervised and unsupervised statistical learning algorithms. Supervised learning pre-specifies the outcome for which the data are to be classified whereas unsupervised algorithms do not have a pre-specified outcome but describe the structure present within a dataset (12). Given that we have limited a priori information on the relationship between variables we will implement several statistical learning algorithm withs different strengths and weaknesses. These will include recursive partitioning regularized regression, and k-means clustering. The reason we use these specific algorithms is that they provide information on the decision-rules underlying the algorithms and are therefore interpretable and may provide insights on underlying mechanisms. We will internally validate the results using bootstrap validation and internal-external validation, based on a temporal split of the data (13).

Data management and analysis

The data in this project come from fourteen distinct sources and a substantial amount of the work comprise combining and harmonizing the data to facilitate analysis in a standard framework. Further challenges include the non-normal distribution of key variables and handling of missing data. However, we have performed similar work for previous data cuts and therefore expect the work to be manageable.

(E) EXPECTED RESULTS

The results from this study is expected to be a provisional algorithm identifying patients at elevated risk of developing PsA. In future research we intend to expand the algorithm by including additional data and perform validation studies. To this end we intend to use the results generated in this project for future grant applications, such as NIH R21 application.

(F) SIGNIFICANCE FOR PSORIATIC DISEASE

An algorithm that identifies patients at high risk of PsA would allow the health care system to monitor these patients and act immediately upon onset of the disease, improving both current quality of life and long-term outcomes.

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